

Complete Summary

GUIDELINE TITLE

EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses.

BIBLIOGRAPHIC SOURCE(S)

Sellebjerg F, Barnes D, Filippini G, Midgard R, Montalban X, Rieckmann P, Selmaj K, Visser LH, Sorensen PS, EFNS Task Force on Treatment of Multiple Sclerosis Relapses. EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses. Eur J Neurol 2005 Dec;12(12):939-46. [55 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
 METHODOLOGY - including Rating Scheme and Cost Analysis
 RECOMMENDATIONS
 EVIDENCE SUPPORTING THE RECOMMENDATIONS
 BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
 QUALIFYING STATEMENTS
 IMPLEMENTATION OF THE GUIDELINE
 INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
 IDENTIFYING INFORMATION AND AVAILABILITY
 DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Relapses of multiple sclerosis

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Internal Medicine
 Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the literature on treatment of multiple sclerosis (MS) relapses to provide evidence-based treatment recommendations

TARGET POPULATION

Patients presenting with relapses of multiple sclerosis (MS)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Intravenous or oral methylprednisolone
2. Plasma exchange
3. Interdisciplinary rehabilitation programme

Note: Intravenous immunoglobulin (IVIG) and natalizumab (withdrawn from market) were considered but not recommended

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment in improving recovery rate, reducing relapse rate, short-term suppression of magnetic resonance imaging (MRI) disease activity, and recovery from optic neuritis
- Adverse effects of glucocorticoid treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The task force searched literature databases (Embase and PubMed) in English for papers using the search terms "multiple sclerosis," "attack," "relapse," "exacerbation," and "treatment" in November 2004. The Cochrane Library and the reference lists of individual papers were searched for studies not identified in the Embase and PubMed searches. Studies of various treatments for patients suffering from relapses of multiple sclerosis (MS) were considered for the guidelines and were rated as class I to class IV studies according to the recommendations for EFNS scientific task forces (see the "Rating Scheme for the Strength of the Evidence" field).

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- a. Randomization concealment
- b. Primary outcome(s) is/are clearly defined
- c. Exclusion/inclusion criteria are clearly defined
- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The results of the literature searches were circulated by e-mail to the task force members for comments. The task force chairman prepared a first draft of the manuscript based on the results of the literature review and comments from the task force members. The draft and the recommendations were discussed during telephone conferences until consensus was reached within the task force. Recommendations were rated from A to C according to the EFNS guidelines for scientific task forces (see the "Rating Scheme for the Strength of the Recommendations" field). Where there was insufficient evidence to support firm recommendations the term "Good practice point" was used.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good practice point: For insufficient evidence to support firm recommendations, the term 'Good practice point' was used.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (Hughes RAC, Barnes MP, Baron J, Brainin M [2001]. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces. *Eur J Neurol* 8:549-550).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

There is consistent evidence from several class I studies and meta-analyses for a beneficial effect of glucocorticoid treatment in relapses of multiple sclerosis (MS). Hence, treatment with intravenous (IV) or oral methylprednisolone in a dose of at least 500 mg daily for 5 days should be considered for treatment of relapses (**level A recommendation**). Treatment with IV methylprednisolone (1 g once daily for 3 days) should be considered as an alternative treatment (**good practice point**; Rieckmann et al., 2004). Treatment with IV methylprednisolone (1 g once daily for 3 days with an oral tapering dose) may be considered for treatment of acute optic neuritis (**level B recommendation**).

There is no evidence of major differences in the efficacy of methylprednisolone treatment given IV or orally in terms of clinical efficacy or side-effects, but prolonged, oral treatment may possibly be associated with a higher prevalence of side-effects. Furthermore, because of the low number of patients included in the available clinical trials, some efficacy differences between the IV and oral route of administration cannot be excluded. The optimal dosage, the specific glucocorticoid to be used, and whether to use a taper after initial pulse therapy have not been adequately addressed in randomized, controlled trials. This implies a need for new, randomized studies assessing risk/benefit ratios and adverse effects of specific glucocorticoids, dose, and route of administration for treatment of MS relapses.

There is insufficient data to clearly define patient subgroups who are more likely to respond to methylprednisolone treatment, but treatment may be more efficacious in patients with clinical, magnetic resonance imaging (MRI), or cerebrospinal fluid (CSF) evidence (increased myelin basic protein [MBP] concentration in CSF) indicating higher disease activity (**level C recommendation**). Administration of treatment in an inpatient or outpatient setting has not been addressed in clinical trials, but consideration could be given to administering the first course of methylprednisolone as an inpatient (**good practice point**).

In patients who fail to respond to therapy with methylprednisolone in the dose range used in the randomized, placebo-controlled trials, treatment with higher doses (up to 2 g daily for 5 days) should be considered (**level C recommendation**; Rieckmann et al., 2004).

Patients with inflammatory demyelination, including patients with MS, who have not responded to treatment with methylprednisolone may benefit from plasma exchange treatment, but only about one-third of treated patients are likely to respond. This treatment regimen should probably be restricted to a subgroup of patients with severe relapses (**level B recommendation**). A randomized, controlled study specifically addressing the effect of plasma exchange in patients with severe relapses of MS not responding to methylprednisolone treatment would be desirable.

A more intense, interdisciplinary rehabilitation programme should be considered after treatment with IV methylprednisolone as evidence from a single trial

suggests that this probably further improves recovery (**level B recommendation**).

There is insufficient data to support the use of intravenous immunoglobulin (IVIG) therapy as monotherapy for relapses of MS. Treatment with intravenous immunoglobulin as an add-on to treatment of MS relapses with methylprednisolone or as monotherapy for acute optic neuritis is not efficacious (**level A recommendation**). Neither is natalizumab as monotherapy efficacious in MS relapses.

Definitions:

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- a. Randomization concealment
- b. Primary outcome(s) is/are clearly defined
- c. Exclusion/inclusion criteria are clearly defined
- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good practice point: For insufficient evidence to support firm recommendations, the term 'Good practice point' was used.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate treatment of multiple sclerosis relapses

POTENTIAL HARMS

- Side effects of glucocorticoid treatment include: reddening of the face, transient ankle swelling, metallic taste in the mouth during infusion, gastrointestinal side effects, minor infections, glucosuria, exacerbation of acne, insomnia, episodes of euphoria, distal paraesthesia, and mild weight gain.
- Pulsed methylprednisolone treatment has marked short-term effects on bone metabolism, and the available studies do not entirely rule out adverse effects on bone structures
- Severe-side-effects of methylprednisolone treatment are rare, but psychosis, acute pancreatitis, and anaphylactoid reactions to intravenous treatment have been reported.
- There is no evidence of major differences in the methylprednisolone treatment given intravenously or orally in terms of clinical efficacy or side-effects, but prolonged, oral treatment may possibly be associated with a higher prevalence of side-effects.

See the original guideline document for more information on adverse effects of glucocorticoid treatment.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Sellebjerg F, Barnes D, Filippini G, Midgard R, Montalban X, Rieckmann P, Selmaj K, Visser LH, Sorensen PS, EFNS Task Force on Treatment of Multiple Sclerosis Relapses. EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses. Eur J Neurol 2005 Dec;12(12):939-46. [55 references] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Dec

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on Treatment of Multiple Sclerosis Relapses

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: F. Sellebjerg, Danish MS Centre, Copenhagen University Hospital, Copenhagen, Denmark; D. Barnes, Department of Neurology, Atkinson Morley's Hospital, Wimbledon, UK; G. Filippini, Unit of Epidemiology and Clinical Trial Centre, Istituto Nazionale Neurologico C. Besta, Milan, Italy; R. Midgard, Department of Neurology, Molde Hospital, Molde, Norway; X. Montalban, Clinical Neuroimmunology Unit, University Hospital Vall d'Hebron, Barcelona, Spain; P. Rieckmann, Department of Neurology, Julius-Maximilians University of Würzburg, Würzburg, Germany; K. Selmaj, Department of Neurology, Medical University of Lodz, Lodz, Poland; L. H. Visser, Department of Neurology, St Elisabeth Hospital, Tilburg, The Netherlands; P. S. Sørensen, Danish MS Centre, Copenhagen University Hospital, Copenhagen, Denmark

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Finn Sellebjerg has received a travel grant and an unrestricted research grant from Pharmacia.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the [European Federation of Neurological Societies Web site](#).

Print copies: Available from Dr Finn Sellebjerg, Danish MS Centre, Department of Neurology, Copenhagen University Hospital, Blegdamsvej 9, DK- 2100 Copenhagen, Denmark; Phone: + 45 3545 2080; Fax: + 45 3545 2684; E-mail: sellebjerg@dadlnet.dk

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the [European Federation of Neurological Societies Web site](#).
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the [European Federation of Neurological Societies Web site](#).
- Continuing Medical Education questions available from the [European Journal of Neurology Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 7, 2006. The information was verified by the guideline developer on January 15, 2007.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the Blackwell-Synergy copyright restrictions.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at <http://www.guideline.gov/about/inclusion.aspx>.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of

developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

© 1998-2008 National Guideline Clearinghouse

Date Modified: 9/15/2008

